

used to analyse the actin staining of the cells. Control cells which were treated only with the vehicle showed the classical actin distribution. After treatment with 0.1  $\mu$ M of bpV(pic) and bpV(phen) morphology remains unchanged even after 24 h. Only concentrations as high as 1 and 10  $\mu$ M over 24 h caused morphological changes.

5 Actin filaments started to re-arrange and cells and nuclei round up. Fibroblasts started to detach and die. These findings indicate that toxicity of the compound starts at  $\mu$ molar concentrations. scale bar = 10  $\mu$ m.

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Figure 7 Effect of  $\mu$ molar bpV(pic) on PKB phosphorylation in the presence of the PI3K inhibitor Ly294002 and the mTOR inhibitor rapamycin: Resting fibroblasts were pre-incubated with the Ly294002 (10  $\mu$ M) and rapamycin (50 nM) for 20 min and 30 min, respectively. This was followed by a treatment with either 10 or 1  $\mu$ M bpV(pic). The PI3K inhibitor ly294002 diminished bpV(pic) induced PKB phosphorylation. In contrast, mTOR inhibitor rapamycin increased phosphorylation

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15 level of PKB.

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Figure 5: Dose dependence of PTEN inhibition, *in vivo*:

Fig 5a Starved fibroblasts that were incubated with different concentrations of all four bpV compounds for 5 min and stimulated for 15 min with 0.5  $\mu$ g/ml insulin showed increasing PKB phosphorylation on Western Blots detecting pSer473 in a concentration-dependent manner. Densitometric analysis resulted in *in vivo* IC<sub>50</sub> values in the lower nano-molar range using NIH Image program.

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Fig 5b Similar experiments accomplished in the PTEN-negative cell line UM-UC did not change the phosphorylation level of Ser473 of PKB at the same concentrations

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